REMARKS

This Amendment is being timely filed, wherein the due date of February 28, 2009 falls on a Saturday. A Petition for Extension of Time is being concurrently filed.

Applicants thank the Examiner for the thorough consideration given the present application.

Request for Clarification of Pending Claims

Applicants respectfully submit that claims 1, 5, 6, 10-13, 16, 27-33, 37, 38, 42, 43, 48-51, 54 and 65-78 are pending in this application. The Examiner did not indicate claims 75-77 are pending. However, these claims depending on claim 1 directly or indirectly were added in the Reply of February 7, 2008 in response to the Restriction Requirement of November 8, 2007. Therefore, these claims are pending and should be examined. Clarification of the status of pending claims 75-77 is respectfully requested.

Status of Claims

Now, claims 1, 5, 6, 10-13, 16, 27-33, 37, 38, 42, 43, 48-51, 54 and 65-78 are being prosecuted. Claims 1 and 33 are independent. Claims 16, 28-33, 37, 38, 42, 43, 48-51, 54, 65-71 and 74 are withdrawn from further consideration.

Claims 1, 5, 6, 10-13, 27, 72, 73 and 75-77 have been amended. Claim 78 is newly added. Claims 2-4, 7-9, 14-15, 17-26, 34-36, 39-41, 44-47, 52-53 and 55-64 were previously cancelled. No new matter has been added. For instance, the amendment to claim 1 is supported by original claim 1, and claims 5, 6, 10-13, 27, 72, 73 and 75-77 are amended to reflect minor

informalities. New claim 78 is supported by original claim 1. Thus, no new matter has been added by way of the present amendments and new claims.

The Examiner is respectfully requested to reconsider the rejections in view of the following remarks.

Issue under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1, 5, 6, 10-13, 27, 72 and 73 under 35 U.S.C. § 112, second paragraph, due to indefiniteness. This rejection is respectfully traversed.

By way of the present submission, this rejection is overcome.

Issue under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 5, 6, 10-13, 27, 72 and 73 under 35 U.S.C. § 103(a) as being obvious over Gao et al. (USP 6,531,139; hereinafter "Gao"). This rejection is respectfully traversed.

The Present Invention and its Advantages

While not conceding to the Examiner's rejection, independent claim 1 has been amended to further emphasize the distinctions of the present invention. Specifically, claim 1 of the present invention is directed to a solubilized paclitaxel composition comprising: 1) 40 to 89.9% by weight of monoolein, 2) 10 to 59.99% by weight of an oil chosen from triglyceride, iodized oil, vegetable oil and animal oil, and 3) 0.01 to 10% by weight of paclitaxel.

In the oral paclitaxel formulation field, formation of paclitaxel precipitation is one obstacle because this precipitation cannot be absorbed into the body. Also, another obstacle of paclitaxel formulation is the lower bioavailability of paclitaxel due to an efflux system of p-glycoprotein in the gastrointestinal tract.

The claimed invention solves these problems by the using a combination of monoolein and an oily component along with paclitaxel (see at least pages 4 and 5 and the Examples of the present specification).

Distinctions between the Present Invention and the Cited Gao Reference

Gao provides a pharmaceutical composition based on the use of a particular oil phase which comprises a lipophilic, pharmaceutically active agent, a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride : monoglyceride), wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length, one or more pharmaceutically acceptable solvents, and one or more pharmaceutically acceptable surfactants.

Specifically, Gao's composition focuses on a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride : monoglyceride).

However, the claimed composition is not rendered obvious in view of the Gao reference for at least the following reasons.

First, Gao's composition comprises diglycerides as main component. In contrast, the claimed composition does not comprise diglycerides as major component because diglyceride compounds are very cytotoxic. Instead, the claimed monoolein exists in the present composition

as a separate main component rather than in the oil. The composition of Gao always has a less amount of monoolein (monoglyceride) than an amount of the diglyceride and thus, the main component in Gao composition is diglyceride rather than monoolein (monoglyceride). Applicants also refer the Examiner to Examples 1-53 of Gao. Accordingly, the claimed composition is patentably distinct from that of Gao in terms of which major components are being utilized.

Second, the ratio of the claimed composition is patentably distinguishable from that of Gao. Specifically, the ratio of oil to monoolein in the claimed invention cannot exceed more than 1.5 times (i.e., 59.99% by weight of oil and 40% by weight of monoolein). In contrast, the ratio of diglyceride to monoglyceride (including monoolein) of Gao's composition is 9:1 to 6:4 (1.5:1). Also, the minimum ratio of monoolein to oil (monoolein : oil) in the claimed composition is more than 1:1.49999 (40% by weight of monoolein : 59.99% by weight of oil). However, in Gao's composition, the maximum ratio of monoolein (monoglyceride) to diglyceride (monoglyceride : diglyceride) is less than 1.5:1. Therefore, the claimed composition is distinct from Gao in terms of the ratio of the main components. Gao also gives no guidance for the skilled artisan to the ratio as claimed.

Third, the Gao composition is characterized by employing solvents and surfactants Specifically, Examples 1-53 of Gao show that the surfactant Cremophor is used in all formulations. In contrast, the present invention does not require such solvents and surfactants (see claims 1 and 78).

Applicants also refer the Examiner to page 1 of the instant specification. It is very well known to one skilled in the art that the solubilizing agent Cremophor causes severe toxic side

effects (hypersensitivity, vasodilation, dyspnea, enervation and high blood pressure) and Cremophor EL may prevent efficient uptake of paclitaxel from the absorption of paclitaxel from the gut. Applicants also refer the Examiner to the abstract of the herein attached article by Bardelmeijer *et al.*, "Entrapment by Cremophor EL decreases the absorption of paclitaxel from the gut," *Journal of Cancer Chemother Pharmacology*, Vol. 49, pp. 119-125 (2002)).

Again, Examples 1-53 of Gao show that the surfactant Cremophor is used in all formulations. Gao gives no guidance for one of ordinary skill in the art to overcome such problems wherein the present invention overcomes such problems.

The present inventors have overcome such problems in the art, as monoolein is a mucoadhesive lipid and paclitaxel is well solubilized in the monoolein compound. However, the paclitaxel/monoolein system precipitates as monoolein changes into the cubic phase when it comes into contact with water. This problem is solved when 10% by weight or more of oil is added to the paclitaxel/monoolein system. Thus, the resulting composition of the present application exerts very high bioavailability (more than 10 times) when orally administered to mice compared to the commercialized paclitaxel formulation Taxol of Bristol-Myers Squibb Company. See at least the Examples in the present specification. This is because the claimed composition does not utilize Cremophor or any other solubilizing agent, wherein the claimed combined monoolein and oil use was not previously known. Thus, the present invention is patentably distinct over Gao's composition.

Further, the mucoadhesive feature of monoolein (of the present invention) has been approved scientifically, wherein the present invention was disclosed and discussed in the journal *Molecular Cancer Therapeutics* ("Efficacy and tissue distribution of DHP107, an oral paclitaxel formulation," Vol. 6(12), pp. 3239-3244 (December 2007)). The *Molecular Cancer Therapeutics* article is herein attached. Applicants respectfully request the Examiner to favorably consider this scientific article when considering the patentability of the claims for the present application.

Example 44 of Gao does disclose a composition having paclitaxel. Still, Gao fails to disclose or suggest any test example regarding oral bioavailability using the composition of Example 44. Accordingly, it is not possible to directly compare oral bioavailability for the two compositions of Gao's composition and the claimed composition.

As discussed above, the claimed composition and Gao's composition are totally different in terms of components and ratio thereof, and among others, the composition of the present application is clearly distinguishable from Gao in that the claimed composition does not comprise an additional solubilizing agent such as Cremophor as a major component. Consequently, the claimed composition cannot be easily expected from Gao. If anything, any modification of Gao in order to achieve the present invention would render the reference inoperable or unsatisfactory for its intended purpose. See MPEP 2143.01(V) and 2143.01(VI).

As the MPEP directs, all the claim limitations must be taught or suggested by the prior art to establish a *prima facie* case of obviousness. *See* MPEP § 2143.03. In view of the fact that the

cited reference fails to teach or fairly suggest the claimed features, a *prima facie* case of obviousness cannot be said to exist.

In light of the above remarks, since the amended independent claim 1 of the present application is believed to overcome the 35 USC § 103(a) rejection, the dependent claims therefrom are also believed to be patentable. Therefore, the Examiner is respectfully requested to withdraw this rejection and allow the pending application.

Non-statutory Double Patenting Rejection

Claims 1, 5, 6, 10-13, 27, 72 and 73 are provisionally rejected on the ground of nonstatutory obviousness double patenting over claims 1-4, 6, 16, 19 and 38 of copending U.S. application No. 10/521,695 (now abandoned). Also, claims 1, 5, 6, 10-13, 27, 72 and 73 are provisionally rejected on the ground of nonstatutory obviousness double patenting over claims 26, 28-31, 41-44, 46 and 47 of copending U.S. application No. 10/521,989. These provisional rejections are respectfully traversed.

First the '695 application has been abandoned, and thus this rejection is rendered moot.

Second, Applicants respectfully submit that the present application (filing date: July 18, 2003) was filed earlier than the above copending applications '695 and '989 (filing dates: July 21, 2003 and July 21, 2003). Accordingly, given that these two copending applications were filed after the claimed invention, the Examiner is respectfully requested to ultimately withdraw the provisional double patenting rejection on a basis of **MPEP § 804 I.B.1.**, which specifically states as follows:

> *"If a provisional nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer..." (emphasis added).*

Therefore, the provisional double patenting rejection should be withdrawn.

Alternatively, Applicants request these rejections be hold in abeyance until this or the copending '989 application issues as a patent.

Conclusion

In view of the above remarks, Applicants believe the application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Craig A. McRobbie, Reg. No. 42,874 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: Monday, March 2, 2009

Respectfully submitted,

By #48,501

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Attachments:

1. Abstract of the present application
2. Bardelmeijer *et al.*, "Entrapment by Cremophor EL decreases the absorption of paclitaxel from the gut," *Journal of Cancer Chemother Pharmacology*, Vol. 49, pp. 119-125 (2002)
3. Hong *et al.*, "Efficacy and tissue distribution of DHP107, an oral paclitaxel formulation," *Molecular Cancer Therapeutics*, Vol. 6(12), pp. 3239-3244 (2007)

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